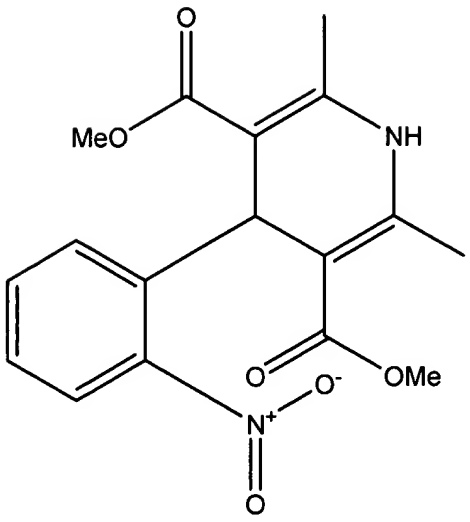
Remarks

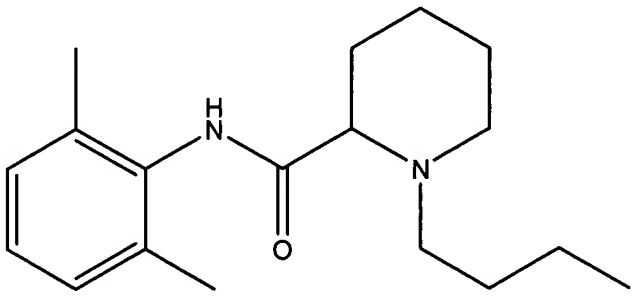
Claims 1, 2, 6-65, and 80-85 are pending in the application. Claims 1, 2, 6-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 stand rejected, and claims 21, 22, 26, 28, 29, 31-36, 38-45, and 85 have been withdrawn from consideration. Claims 6, 82, and 83 have been canceled. New claims 86-97 have been added, and support for these new claims can be found in original claims 1, 13, 25, 28, 30, 37, 46, 47, 50, 52, and 56, in the examples (page 33-36, Results), and in the specification (page 12, lines 1-2; page 15, lines 5-21; page 17, lines 10-18; and page 16, line 3). No new matter has been added by the present amendments. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 102(a), as being anticipated by Bot *et al.* (WO 00/00215). Claims 1, 2, 6, 7, 13, 17-20, 23-25, 27, 28, 30, 37, 46, 48-53, 57-60, 62-65, and 80-85 remain rejected under 35 U.S.C. § 102(a) as being anticipated by Bot *et al.* (WO 00/00215). The Examiner states that the Declaration of Dr. Kohane submitted with the Response dated July 13, 2004 is not commensurate with the scope of the claims. The Examiner continues that the claims are broader in scope than the Declaration because Exhibit B of the Declaration describes encapsulating only nifedipine and bupivacaine. Applicant respectfully disagrees as one of ordinary skill in the art reading the evidence presented in Exhibit B would understand that any small molecule drug could be encapsulated in a lipid-protein-sugar particle. Therefore, the Declaration of Dr. Kohane as previously filed *does* support the full breadth of the claims.

The evidence presented with the Declaration supports the pending claims reciting a solid microparticle of an agent encapsulated in a matrix comprising lipid, protein, and sugar. The calcium channel blocker nifedipine and the anesthetic bupivacaine were only exemplary agents incorporated into lipid-protein-sugar particles. It should be noted that these two agents are from two different classes of drugs and furthermore that these two agents have different chemical structures as shown below:



Nifedipine
dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate



Bupivacaine
1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide

These two drugs merely represent two examples of small molecules which can be encapsulated in the inventive particles. Demonstration that these agents could be incorporated into the particles established that other small molecule agents could also be encapsulated in lipid-protein-sugar microparticles. Furthermore, the specification also establishes that proteins may also be incorporated into lipid-protein-sugar microparticles. By definition, the lipid-protein-sugar particles of the present invention contain proteins. Addition of protein as an agent, therefore, would not change the fact that the inventive particles comprise a lipid, a protein, and a sugar. Therefore, lipid-protein-sugar particles with protein as the agent are inherently enabled by the specification. In summary, the Declaration is evidence that the claimed invention was reduced to

practice before January 6, 2000, and the Bot reference should be removed as prior art against the present application. Applicant respectfully requests that the rejection be removed.

Furthermore, the Examiner maintains that Bot teaches the particles of the present invention. According to Bot, the Bot microparticles "provide for the attenuation or reduction of hydrogen and liquid bonding" (Page 29, lines 4-5). Bot further states that the use of hydrophilic compounds (such as lactose) promotes hydrogen and liquid bonding and that "preferred excipients include hydrophobic surfactants" (page 29, lines 8-12). In light of this teaching, Bot cannot be said to teach microparticles comprising sugars (including mono–, di–, or poly–saccharides, lactose, dextran, starch, cellulose, or chitin) because sugars are hydrophilic. Even though Bot includes sugars in the laundry list of acceptable particle components, Bot explicitly teaches away from microparticles comprising hydrophilic compounds, such as sugars. The particles of the present invention contain sugars; therefore, Bot cannot teach the particles of the present invention and actually teaches away from the claimed particles. Applicant respectfully requests that the rejection be removed.

II. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). Claims 1, 2, 6, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 maintains the rejection under 35 U.S.C. 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). Examiner states that the particles of the present invention are obvious in view of Bernstein. Applicant disagrees. The specification of Bernstein includes an extensive laundry list of possible matrix components, but only one particle was actually made: PLGA-lipid. Therefore, Bernstein does not teach the microparticles of the present invention because the specification of the present application teaches away from the use of synthetic polymers traditionally used in preparing microparticles for drug delivery. The present invention teaches the use of biocompatible components, such as lipids, proteins, and sugars, in the matrix of microparticles. Specifically, drug delivery particles containing PLGA elicited a statistically significant increased inflammatory response at the site of injection compared to lipid-protein-sugar particles (page 52, sections entitled "Tissue reaction two weeks after injection" and "Tissue reaction eight weeks

after injection"). In addition, PLGA particles were found at locations where they were not intentionally placed (page 54, section entitled "*Other findings on dissection*"). There were no similar findings in rats injected with LPSPs. Given these negative consequences of administering a drug via microparticles comprising PLGA, the present specification teaches away from particles which contain synthetic polymers or are primarily made of synthetic polymers. Furthermore, the particles prepared by Bernstein do not contain sugar or protein. Therefore, Bernstein does not enable the preparation of the microparticles of the present invention, which comprise lipid, protein, and sugar. Applicant respectfully requests that the rejection be removed.

Although a synthetic polymer, such as PLGA, could be used as a component in the microparticle of the present invention, it is not the sole component, nor is it a primary component. Instead, the amount of synthetic polymer is reduced by the use of other biocompatible components, such as lipids, proteins, and sugars. This is not the case for the PLGA-lipid particles taught by Bernstein.

With respect to claims 6, 82, and 83, the Examiner has stated that the previous amendment, in which lipids were excluded from the matrix of the microparticles, constitutes a distinct invention and is subject to restriction/election. Without conceding the Examiner's point, Applicant has canceled claims which contain this exclusion. Therefore, Applicant submits that the cancellation of these claims renders the Examiner's rejection moot.

III. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345) and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). Claims 8-11 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345), and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). As discussed above, Bernstein does not render obvious the microparticles of the present invention. The present specification, in fact, teaches away from particles containing primarily PLGA. Therefore, even if there is a teaching or suggestion to combine Goldenheim and Bernstein, the combination would not render the claimed invention of claims 8-11 obvious

because even the references when combined do not teach a matrix comprising solely or primarily PLGA. Applicant respectfully requests that the rejection be removed.

IV. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215).** Claims 47, 54-56, and 61 stand rejected by the Examiner under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215). As discussed above, the Bot *et al.* reference is not a prior art reference under 35 U.S.C. § 102(a) given the Declaration submitted by Dr. Kohane previously. Applicant submits that the Declaration is evidence that the invention as claimed was conceived and reduced to practice before the publication of Bot. The Declaration taken in the context of the art and the present specification is commensurate with the scope of the claims because other agents besides nifedipine and bupivacaine could be incorporated into the inventive microparticles. Applicant, therefore, requests that this rejection be removed.

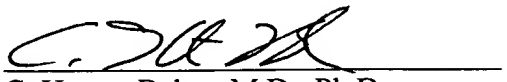
V. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081).** Claims 8-11 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081). As discussed above, the Bot *et al.* reference is not prior art under 35 U.S.C. § 102(a) by the Kohane Declaration. Without the teachings of Bot *et al.*, the Examiner has not established a *prima facie* case of obviousness; therefore, Applicant requests that the rejection be removed.

Applicant thanks the Examiner for a telephone conference on August 22, 2006 regarding this case at which the present rejections and cited art were discussed. Applicant further thanks the Examiner for the Interview Summary dated August 29, 2006 which describes the telephone conference.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,



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